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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,435	08/01/2001	Yuriy M. Dunayevskiy	HKI-106AX	6450

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WEINGARTEN, SCHURGIN, GAGNEBIN & LEOVICI LLP
TEN POST OFFICE SQUARE
BOSTON, MA 02109

EXAMINER

EPPERSON, JON D

ART UNIT	PAPER NUMBER
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1639

DATE MAILED: 03/31/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary*File Copy*

Application No.

09/920,435

Applicant(s)

DUNAYEVSKIY ET AL.

Examiner

Jon D Epperson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 January 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-22 is/are pending in the application.
- 4a) Of the above claim(s) 15-20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-14, 21 and 22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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DETAILED ACTION

Please note: The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to **Group Art Unit 1639**.

Status of the Application

1. Receipt is acknowledged of a Response to a Restriction Requirement, which was dated on January 28, 2003 (Paper No. 6).

Priority Claims

2. The priority filing date of February 12, 1999 for application 60/119,966 is acknowledged.

Status of the Claims

3. Claims 1-22 are pending in the present application.
4. Applicant's response to the Restriction and/or Election of Species requirements in Paper No. 6 is acknowledged (Applicants elected Group I i.e., claims 1 (in part), 2-14, 21 and 22 with traverse) and claims 1 (in part), 15-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim (see below i.e., Response to Restriction and/or Election of Species).

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5. Therefore, claims 1 (in part), 2-14 and 21-22 are examined on the merits in this action.

Response to Restriction and/or Election of Species

6. Applicant's election of Group I (claims 1 (in part), 2-14 and 21-22) in Paper No. 6 with traverse is acknowledged.

7. The traversal is on the ground(s) that "the claims encompass one group without burdening the Examiner with completely different searches. The inventive technical features comprised in Group I and II claims are not separate and distinct. Claims represented in Group II are directed to using a competitive assay by adding a known binding ligand to the same steps recited in the method claims in Group I. In addition of a competitive ligand is another way for determining the specificity of an unknown hit. These two methods are not mutually exclusive."

8. These arguments were fully considered but were not found persuasive. As stated in the Restriction Requirement dated October 24, 2002 (see Paper No. 5), these inventions (Groups I-II) have acquired a separate status in the art as shown by their different classification and/or divergent subject matter. The different methods would require the use of different method steps, different reagents and/or will produce different results. Therefore, the Examiner contends that the search will not be coextensive and will constitute an undue search burden for the Office.

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9. Applicant's election of species in Paper No. 6 is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election of species has also been treated as an election without traverse (MPEP § 818.03(a)).

10. As a result, the restriction requirement and/or election of species is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

11. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98 (b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on the form PTO-892, they have not been considered.

12. The references listed on applicant's PTO-1449 form have been considered by the Examiner. A copy of the form is attached to this Office Action.

Specification

13. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1-14 and 21-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. For **claims 1 and 14**, the term “natural” is indefinite and/or unclear. The term is vague and indefinite because it is not clear how one of ordinary skill in the art would be able to identify a “natural” sample from an “unnatural” sample. Absent of a teaching of all naturally occurring samples, one would not be able to determine which were or were not made by a natural process because both the “natural” and “unnatural” samples would have the same structures i.e., you couldn’t tell just by looking at them. Consequently, it is not possible to determine the metes and bounds of the invention as claimed despite the examples provided applicants (e.g., see specification, page 8, last paragraph). Therefore, claims 1 and 14 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

B. For **claim 3**, the phrase “having a molecular weight of about 1,500 or less” is vague and indefinite because the units have not been stated i.e., the Examiner recommends the phrase “having a molecular weight of about 1,500 daltons or less.”

Consequently, it is not possible to determine the metes and bound of the claimed invention. Therefore, claims 3 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

C. For **claim 13**, the phrase “comparing the analytical results of step (6) with a reference standard” is vague and indefinite because claims 1, 4 and 5 do not refer to a “step (6)” to which claim 13 depends. Consequently, it is not clear what is being referenced. Correction is requested. Therefore, claim 13 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

D. For **claim 14**, the entire claim is unclear. For example, it is not clear how subjecting either a sample of the protein target alone or a mixture of the protein target with a non-target-binding natural sample could function as a reference standard because it is not clear what is being referenced. Clarification and/or correction is requested. Therefore, claim 14 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

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15. Claims 1-14 and 21-22 are rejected under 35 U.S.C. 102(e) as being anticipated by Nash et al (US Patent No. 6,207,861) (Date of Patent is **March 27, 2001**).

For *claim 1*, Nash et al (see entire document) discloses a method for identifying members of a mass-coded combinatorial library which are ligands for a biomolecule wherein said biomolecule can be a protein that anticipates claim 1 (see Nash et al, column 2, paragraph 3). For example, Nash discloses mixing a protein target and a natural sample in solution to form a reaction mixture and incubating said mixture under conditions that will allow complex formation (see Nash et al, column 2, lines 30-36), which anticipates claim 1 (1) and (2). Nash discloses passing the reaction mixture through a first size-exclusion column medium that removes from the reaction mixture any small molecular weight compounds (see Nash et al, column 2, lines 36-38; see also column 13, lines 54-67; see also column 15, last paragraph; see also Examples 4-5 and 7-8). Nash discloses subjecting the size-excluded reaction mixture to conditions promoting dissociation of any ligand/target complex into free ligand and free target (see Nash et al, column 2, lines 38-39). Nash discloses subjecting the reaction mixture to a second size exclusion medium (see Nash et al, column 2, lines 47-40, please note that Applicants "comprising" language does not preclude the addition of a second library).

Claim Rejections - 35 USC § 103

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16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all

obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 1-14 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaur et al (Kaur, S.; McGuire, L.; Tang, D.; Dollinger, G.; Huebner, V. "Affinity Selection and Mass Spectrometry-Based Strategies to Identify Lead Compounds in Combinatorial Libraries" *Journal of Protein Chemistry* **1997**, *16*, 5, 505-511) (see IDS) and Van Breemen et al (Van Breemen, R. B.; Huang, C. -R.; Nikolic, D.; Woodbury, C. P.; Zhao, Y. -Z.; Venton, D. L. "Pulsed Ultrafiltration Mass Spectrometry: A New Method for Screening Combinatorial Libraries" *Anal. Chem.* **1997**, *69*, 2159-2164).

For *claim 1*, Kaur et al (see entire document) teaches a method for identifying lead compounds in a combinatorial library wherein a target protein is mixed with a

combinatorial library of potential ligands under conditions that allow for complex formation using hyphenated SEC-LC(reverse phase)-ESI technology (see Kaur et al, section 2.2; see also figure 1; see also first paragraph under Results and Discussion section). First, Kaur et al discloses passing the reaction mixture through a first size-exclusion column to remove small molecular weight compounds that are less than a first preset value (see Kaur et al, paragraph bridging pages 506-507). Second, Kaur et al discloses subjecting the size-excluded reaction mixture to conditions promoting dissociation of any ligand/target complex into free ligand and free target via a reverse-phase LC column (see Kaur et al, page 507, column 1, paragraph 1).

For *claims 2-3*, Kaur et al shows the separation of molecules that are in the range of 350-800 daltons (see Kaur et al, page 507, column 2, paragraph 1; see also figures 2a-c).

For *claim 4*, Kaur et al discloses a Pharmacia HR 10/10 size exclusion HPLC column (see Kaur et al, page 506, section 2.2).

For *claim 5*, Kaur et al discloses the use of 50/50/1 to 30/70/1 water/acetonitrile/acetic acid (see Kaur et al, page 506, column 2, paragraph 1).

For *claims 13-14*, Kaur et al discloses referencing the masses of the ligands identified with those predicted in the compound library (see Kaur et al, page 507, column 1, paragraph 1).

For *claims 21-22*, Kaur et al discloses the use of CID-MS/MS to confirm the identity and structure of any potential ligands (see Kaur et al, page 507, column 1, paragraph 1).

The prior art teachings of Kaur et al differ from the claimed invention as follows:

For *claims 1, 5-12*, Kaur et al is deficient in that it does not teach the use of a second size exclusion medium. Kaur et al only teaches the use of a reverse-phase LC cartridge coupled to an electrospray mass spectrometer i.e., an LC-MS (note MS represents applicants elected method of detection i.e., mass spectrometry) step to dissociate the ligand/target complex instead of the required SEC-MS (see Kaur et al, page 507, column 1, paragraph 1).

However, Van Breemen et al teaches the following limitations that are deficient in Kaur et al:

For *claim 1 and 5-12*, Van Breemen et al (see entire document) teaches the use of a hyphenated ultrafiltration-mass spectrometry technique i.e., ultrafiltration-MS that can be used as a substitute for LC-MS (see Van Breemen et al, page 2160, column 1, last paragraph, “[a] liquid chromatograph-electrospray mass spectrometer (LC-MS) was used as the screening apparatus, except that an ultrafiltration chamber was substituted for the HPLC column”). Furthermore, Van Breemen et al discloses the use of organic solvents and acids to disrupt the protein-ligand complex (see Van Breemen et al, Experimental section; see also page 2163, column 2, paragraph 1). Van Breemen et al also discloses the use of an ultrafiltration YM-10 (from Amicon) membrane and states that the cutoff of the membrane should be selected so as to retain the target protein i.e., if the protein is 40,000 then the cutoff must be less than 40,000 (e.g., a 10,000 molecular weight cutoff was used for the 41,250 MW adenosine deaminase target protein).

It would have been obvious to one skilled in the art at the time the invention was made to substitute the “ultrafiltration-MS” as taught by Van Breemen et al for the “LC-MS” portion of the hyphenated SEC-LC-MS method as taught by Kaur et al (i.e., a hyphenated SEC-ultrafiltration-MS method would result after substitution) because Van Breemen et al explicitly states that the ultrafiltration-MS can be substituted for LC-MS and the method of Kaur et al (see Van Breemen, page 2161, column 1, paragraph 3, “A liquid chromatograph-electrospray mass spectrometer (LC-MS) was used as the screening apparatus, except that an ultrafiltration chamber was substituted for the HPLC column [i.e., ultrafiltration-MS was substituted for LC-MS]”). Furthermore, the two references (i.e., Van Breemen et al and Kaur et al) represent overlapping subject matter i.e., both are drawn to methods for identifying ligands to target proteins in natural samples using solution phase size exclusion techniques (see abstracts and introductory sections to both papers). Furthermore, one of ordinary skill in the art would have been motivated to substitute the ultrafiltration method as taught by Van Breemen et al for the reverse-phase LC method as taught by Kaur et al because Van Breemen teaches that unlike the method of Kaur et al the target protein could be reused in the Van Breemen method which would enable a considerable cost savings for precious target protein samples (see Van Breemen et al, page 2164, last paragraph, “Unlike these other mass spectrometry-base screening methods, pulsed ultrafiltration mass spectrometry allows the solution-phase receptor to be recovered or reused, which is a distinct advantage when the receptor protein is expensive or in short supply. In addition, only pulsed ultrafiltration mass spectrometry allows library compounds to be extracted from a dilute solution and

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concentrated onto the receptor molecule, which overcomes common library solubility limitations"). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Van Breemen et al teaches a specific example wherein the ultrafiltration was successfully used to replace LC (see Van Breemen et al, entire document, especially page 2160, column 1 paragraph 3; see also Results and Discussion Section).

Contact Information

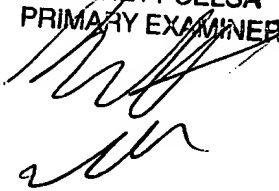
19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (703) 308-2423. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

20. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

21. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-2439.

Jon D. Epperson, Ph.D.
March 24, 2003

BENNETT CELSA
PRIMARY EXAMINER



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